Biological drugs in the treatment of atopic dermatitis – current recommendations of the Polish Dermatological Society, the Polish Society of Allergology, the Polish Pediatric Society and the Polish Society of Family Medicine

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Abstract

Atopic dermatitis (AD) is secondary to genetic, immunological and microbiological disorders as well as epidermal barrier defects, which are the main targets of therapy. The disease proceeds with periodic exacerbations. Its development and course are influenced by numerous environmental and individual factors. In recent decades, in industrialized countries, there has been a threefold increase in the incidence of AD. There is also an increasing number of cases resistant to topical treatment. Effective treatment of AD should provide control of clinical symptoms, prevent exacerbations and improve the quality of life of patients. The multifactorial etiopathogenesis and various endotypes and phenotypes of AD justify the tendency to optimize and personalize the therapy. Currently, we recommend the use of dupilumab for the treatment of patients from 12 years of age with moderate and severe atopic dermatitis, who do not respond to topical treatment.

Key words: biological drugs, dupilumab, atopic dermatitis, therapeutic recommendations.

Introduction

Atopic dermatitis (ICD-10 L20) is a chronic disease that affects mainly children (10–20%) and lasts until adulthood in about 1/5 of this group [1]. The prevalence of AD in adults has been estimated at 2.1–4.9% [2]. In adulthood, the disease appears for the first time in one of four adult patients suffering from AD [3].

In over 60% of cases, there is an increased risk of developing atopic symptoms from other organs. Atopic der-

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matitis is the first step in the atopic march, in the course of which the following may develop: food allergy (15%), allergic rhinitis (34%) and bronchial asthma (20–35%). Very severe and persistent itching, hypersensitivity and visible skin inflammation and stigmatization significantly reduce the quality of life and are often the cause of anxiety, sleep disorders, absenteeism at school and work, social isolation and, consequently, depression, mental illness and even suicidal thoughts. Children with AD are more likely to develop abdominal obesity and arterial hypertension [4, 5].

Skin diseases associated with atopic dermatitis include ichthyosis (ichthyosis vulgaris), infectious diseases such as impetigo and herpetic eczema (eczema herpeticum), and immune diseases: alopecia areata and vitiligo (vitiligo). White dandruff (pityriasis alba) and keratosis pilaris are common in patients with AD [6, 7].

Cutaneous lymphoma may develop in adults with severe AD. Moreover, the relationship between AD and obesity, metabolic syndrome, cardiovascular diseases and osteoporosis has been described [8, 9].

Biological drugs in atopic dermatitis

Modern treatment of AD involves two groups of medicinal products: monoclonal bodies that act precisely to inhibit specific cytokines or their receptors, and agonists or antagonists of small molecules. Action of those latter is even broader. It is now known that, in addition to the defect in the epidermal barrier and disorders of the skin microbiota homeostasis, AD is immunologically characterized by abnormal activity of the Th2 cellular system expressed by excessive activity of cytokines such as IL4, IL13, cytokines secreted by Th17, Th22, Th1 lymphocytes and cytokines derived directly from the damaged epidermis (IL33, TSLP, IL25) [10–12]. Involvement of the Th2 cellular system seems to be the leading and ethnically or pheno-/endotypically independent factor. Which means it affects every patient with AD [13–15]. Hence, targeting the treatment to suppress the Th2 cellular system seems perfectly justified. In 2017, the FDA and EMA approved the drug dupilumab, the first biological drug in AD for the treatment of its moderate and severe form.

Dupilumab

Dupilumab is a human IgG4 monoclonal antibody directed against the alpha subunit of the IL-4 receptor (IL-4Rα), thanks to which it blocks both IL-4 and IL-13. The current approval of the drug covers the treatment of moderate to severe AD in patients aged 12 years and over.

Efficacy of dupilumab therapy in children from 6 years of age, adolescents and adults

The efficacy and safety of dupilumab as a monotherapy or administered concomitantly with topical glucocorticoids in adults were assessed in randomized, double-blind, placebo-controlled phase 2b trials in 452 patients, trials LIBERTY AD SOLO 1 and LIBERTY AD SOLO 2 in 1379 adult AD patients, and 740 patients in the LIBERTY AD CHRONOS trial lasting up to 52 weeks [16–19]. The trials enrolled patients with a prior inadequate response to topical medications with severe to moderate AD as assessed by Investigator's Global Assessment (IGA) score ≥ 3, eczema area and severity index (EASI), Eczema Area and Severity Index ≥ 16 and Body Surface Area (BSA) ≥ 10%. Dupilumab significantly improved the objective and subjective symptoms of AD and quality of life in patients with moderate to severe AD. A reduction in the SCORAD and EASI-75 scores, as well as a reduction in the severity of pruritus, anxiety/depression and sleep disorders have been observed in adults [16–21]. The drug is administered subcutaneously at the first dose of 600 mg, followed by the dose of 300 mg s.c. every 2 weeks.

In the group of young people over 12 years of age, 251 patients with a mean age of 14.5 ±1.7 years were randomized. Majority of these patients had other allergic diseases such as asthma, food allergy, and allergic rhinitis. Dupilumab significantly improved signs, symptoms and quality of life in adolescents with moderate to severe AD, with an acceptable safety profile. Effectiveness of the drug administered every 2 weeks was definitely higher than every 4 weeks [22]. Results were obtained and evaluated after 16 weeks of treatment. The drug is administered subcutaneously at the dose of 200 mg in children weighing < 60 kg or 300 mg for body weight ≥ 60 kg, every 2 weeks or 300 mg every 4 weeks.

Data are available from the phase III clinical trial of dupilumab treatment with concomitant topical GCSs treatment in children aged 6–11 years with severe AD, with inadequately controlled topical treatment [23]. Three hundred sixty seven children were enrolled in the 16-week study. Dupilumab was effective and improved the quality of life of patients in this age group. Taking into account the effectiveness and side effects, the optimal dose was 300 mg every 4 weeks for children weighing less than 30 kg and 200 mg every 2 weeks for children weighing 30 kg or more [23]. Data from registries and descriptions of patients treated with dupilumab, in real life, apart from clinical trials, indicate comparable results to those obtained during clinical trials [24–29].

Adverse reactions during dupilumab therapy in children from 6 years of age, adolescents and adults

The most common adverse reaction observed in 22.1% of dupilumab users in adult clinical trials are conjunctivitis and blepharitis [30, 31]. In observations during the use of the drug outside clinical trials, this complication reaches the level of 38.2% [26]. The suggested treatment is the use of artificial tears, drops with tGCS (fluorometholone 0.1%), topical calcineurin inhibitors (tCI) applied to the eyelids in moderate cases, and eye

drops or ointments containing cyclosporin or tacrolimus in severe forms [31, 32].

Most cases of conjunctivitis are transient and can be successfully treated by continuing the therapy with dupilumab [29]. In terms of rates of infection, it was found that it was similar in adult patients receiving dupilumab and placebo. Dupilumab did not increase the risk of infection, nasopharyngitis, or upper respiratory tract infection, and the systemic use of anti-infective agents was lower in the dupilumab group. Fewer serious/severe bacterial infections and other non-herpetic skin infections were observed among patients using dupilumab [33]. Among the side effects with long-term use of dupilumab, paradoxical erythema of the face, décolleté and neck, usually after 10–39 weeks of using dupilumab, has been reported [34, 35]. In the group of adolescents > 12 years of age treated with dupilumab, a higher percentage of conjunctivitis and reactions at the injection site and lower rates of non-herpetic skin infections were observed [21]. Children with severe AD, aged 6–11 treated with dupilumab presented more frequent conjunctivitis and injection site reactions than the placebo group [23]. More research is needed in the pediatric group.

Laboratory tests, monitoring during dupilumab therapy

According to the evaluation of the results of available clinical trials conducted in the adult group, there is no need for laboratory monitoring during dupilumab therapy [36]. However, before and during dupilumab therapy (after 16 weeks and then every 3 months), we suggest performing basic tests (complete blood count with smear, AST, ALT, creatinine, urea, CRP). Before starting the therapy, we additionally recommend a pregnancy test in women of childbearing age, ECG and chest X-ray examinations (Table 1).

Table 1. Diagnostic procedures before and during the treatment with dupilumab

Procedures before start of the therapy with dupilumab:
General health assessment based on the medical history Assessment of symptoms intensity with the EASI score Blood cell count with smear clinical chemistry: creatinine, urea, CRP, transaminases (ALT, AST) X-ray of the chest ECG Pregnancy test in women of childbearing potential
Procedures after 16 weeks of the therapy, and then every 3 months (±7 days):
General health assessment based on the medical history Assessment of symptoms intensity with the EASI score Blood cell count with smear Clinical chemistry: creatinine, urea, CRP, transaminases (ALT, AST)

Data on long-term safety in children and adolescents are time-limited and the size of the pediatric group indicates a need to extend the research in these age groups.

Safety of long-term dupilumab therapy in children from 6 years of age, adolescents and adults

Long-term safety of up to 3 years of use of dupilumab has been established for adults [37, 38]. In the group of children aged 12–17 years, safety data covers up to 52 weeks of treatment with dupilumab [39]. In this group, as well as in the group of 6–11-year-olds there are currently no results of studies lasting more than 1 year [23, 39].

Dupilumab combined with other drugs used in atopic dermatitis

Dupilumab should be combined with the daily use of emollients and, if necessary, may be combined with topical anti-inflammatory drugs [40].

Recommendation

The use of dupilumab is recommended in patients from 12 years of age with moderate to severe AD (EASI ≥ 16, SCORAD ≥ 25) who do not respond to local treatment. The duration of therapy depends on the resolution of the disease and the decision of the treating physician. Dupilumab may be self-administered subcutaneously by the patient or his caregivers at home (Table 2).

If there is no improvement after 16 weeks of dupilumab use (assessed as not achieving at least a 50% reduction in the EASI score), treatment with this drug should be discontinued.

Other biological drugs – monoclonal bodies in the treatment of atopic dermatitis

Randomized, double-blind, placebo-controlled clinical trials are currently underway to evaluate the efficacy and safety of other biologics in adult patients with mild and severe AD. There are test results for monoclonal antibodies such as: tralokinumab, lebrikizumab (anti-IL-13),

Table 2. Dosage of dupilumab for subcutaneous administration to patients with atopic dermatitis

Patients	**Initial dose**	**Subsequent doses (every 2 weeks)**
Adolescents from 12 to 17 years:		
Below 60 kg	400 mg (two s.c. injections a' 200 mg)	200 mg
60 kg or more	600 mg (two s.c. injections a' 300 mg)	300 mg
Adults	600 mg (two s.c. injections a' 300 mg)	300 mg

nemolizumab (anti-IL-31Rα), fezakinumab (anti-IL-22), etokimab (anti-IL-33) and tezepelumab (anti-TSLP).

Lebrikizumab

Lebrikizumab is an IL-13 binding monoclonal antibody. A randomized, placebo-controlled phase II clinical trial enrolled 209 adult patients with severe to moderate AD in whom topical glucocorticoids (tGCSs) were ineffective. The drug efficacy and safety were assessed after 12 weeks. The drug was administered to patients at the dose of 125 mg every 4 weeks – subcutaneously, and at the same time the use of tGCSs was allowed. Lebrikizumab led to significant clinical improvement and was well tolerated [41].

Tralokinumab

Tralokinumab is an IL-13 binding monoclonal antibody. The results of the phase 2b clinical trial were published in 2019. The study included 204 adult patients with moderate and severe AD. The treatment was combined with tGCSs. Results summarized after 12 weeks of therapy indicated that the treatment with tralocanumab was associated with an early and sustained improvement in AD symptoms with an acceptable safety and drug tolerance profile [42].

Nemolizumab

Given the pathogenesis of pruritus in AD, nemolizumab – an antibody directed against the IL-31 receptor – gave hope for improvement in this persistent symptom.

In a phase 2 study in 264 adult patients with severe and moderate AD who were not treated with tGCSs, 12 weeks of nemolizumab therapy brought a significant reduction in pruritus in treated patients. However, a limited number of patients enrolled in the study and a short evaluation period (12 weeks at the summary stage) did not allow the authors to draw conclusions about adverse effects [43]. Another phase 2b study with nemolizumab 10 mg, 30 mg and 90 mg administered subcutaneously every 4 weeks with 226 patients was summarized after 24 weeks of treatment. Nemolizumab produced a rapid and sustained improvement in cutaneous inflammation and itching with maximum efficacy seen with the 30 mg dose. The safety profile of nemolizumab was assessed as acceptable [44]. The drug has also been evaluated in a long-term study in 264 patients with moderate to severe AD. Nemolizumab used for up to 64 weeks was effective and well tolerated. Similar responses in improvement of EASI-75 score were observed in the treated and placebo groups. However, the pruritus was significantly reduced in patients treated with the active drug [45].

Fezakinumab

Fezakinumab, an anti-IL-22 antibody, was evaluated in a Phase 2a clinical trial in 60 patients with moderate to severe AD not controlled with tGCSs. The study ran for 20 weeks and results were summarized at week 12. Fezakinumab was well tolerated and provided a long-term clinical improvement after the last drug administration [46].

Etokimab

Etokimab, an anti-IL-33 monoclonal IgG1 antibody. A phase 2a study was conducted in 12 adult patients with moderate to severe AD. Patients received etokimab once. Rapid and sustained clinical improvement was observed. 83% of patients reached EASI50, and 33% reached EASI75, with a reduction in peripheral blood eosinophils on day 29 after dosing. These results confirm the role of IL-33 in modulation of the inflammatory cascade in atopic skin and confirm the therapeutic potential of IL-33 in the treatment of AD [47].

Tezepelumab

Tezepelumab is a monoclonal antibody directed against thymic stromal lymphopoietin (anti-TSLP). Considering the role of TSLP in the pathogenesis of AD, this cytokine derived from damaged keratinocytes raises high hopes as a therapeutic target. Results of the Phase 2a study involving 113 patients with moderate to severe AD who used tGCSs along with the study drug were summarized in weeks 12 and 16 of treatment with a subcutaneous dose of 280 mg of the drug administered every 2 weeks. EASI50 was achieved by more patients treated with tezepelumab than with placebo. However, these differences were not statistically significant, although an increase in the proportion of responders at the week 16 of the study was observed [48].

OX40 molecule antagonists

OX40 is a costimulatory receptor on activated T cells (CD4). The fully human anti-OX40 monoclonal antibody was tested under the names KHK4083 and GBR830.

A phase 1 study evaluated the pharmacokinetics and immunogenicity of KHK4083 in 22 Japanese patients with moderate and severe AD [22]. The drug was administered at the dose of 10 mg/kg intravenously on days 1, 15 and 29 and patients were followed up to day 155. Multiple intravenous infusions of KHK4083 had an acceptable security profile. After the end of treatment with KHK4083, a sustained improvement in AD symptoms was observed [49]. It is interesting whether these results can be extrapolated to the European population in the face of hypotheses/theories of differentiation of AD endotypes also in the ethnic context. GBR 830 was also evaluated among US patients with moderate to severe AD in a phase 2a study that enrolled 64 patients. More than 40 people received the drug on days 1 and 29, and in 40 cases its effect was assessed in histopathological preparations. Two doses of GBR 830 given 4 weeks apart

were well tolerated and induced resolution of tissue and clinical changes by day 71, confirming the therapeutic potential of this drug [50]. Results of studies with the monoclonal bodies described above refer to the second phase in adults. A clear limitation is the low size of study groups. Results of the third phase of this research may be expected soon.

Agonists and antagonists of small molecules

JAK-STAT inhibitors are a group of drugs that have been intensely studied in AD in recent years. These drugs are less selective than monoclonal bodies. They block the activation of Janus kinases, translocating the signal to the cell nucleus and, consequently, the transcription of many pro-inflammatory cytokines. Results of research completed so far are promising. These drugs are mainly used orally or topically.

Abrocitinib

Abrocitinib is a selective JAK 1 inhibitor. A Phase 2b, randomized, double-blind, placebo-controlled (RDBPC) study was conducted in 267 adult patients with moderate to severe AD with insufficient response or contraindication to topical treatment. The results of the study, summarized after 12 weeks of treatment, showed that abrocitinib administered orally once daily was effective and well tolerated for short term use in adults with moderate to severe atopic dermatitis. However, additional studies were necessary to assess the long-term efficacy and safety of the drug [51]. This year, the results of the phase III JADE study were published [52]. Three hundred and eighty-seven adolescent patients from 12 years of age and adults with moderate and severe atopic dermatitis used the drug at the dose of 100 mg or 200 mg. The study is still ongoing, but results summarized after 12 weeks of therapy showed the clinical effect of EASI75 for both doses of the drug. Oral once daily monotherapy with abrocitinib was effective and well tolerated in adolescents and adults with moderate to severe atopic dermatitis [52].

Baricitinib

Baricitinib is a selective inhibitor of JAK 1 and JAK2. A phase 2 study, RDBPC, was conducted in 124 adult patients with moderate to severe AD. The drug at the dose of 4 mg and 2 mg was used orally with the possibility of simultaneous application of tGCSs. After 16 weeks of the study, a significant reduction in the severity of clinical symptoms of AD and an improvement in the quality of life was achieved. It is worth noting that improvement in clinical symptoms, including reduction of itching, was noted already in the first week of treatment in patients taking the drug at the dose of 4 mg. No serious adverse events were observed [53]. Results of the Phase III study have been published this year. The BREEZE-AD1 arm included 624 patients, and the BREEZE-AD2 arm included 615 patients with moderate and severe AD. Results of the study were collected after 16 weeks of treatment with baricitinib at doses of 1 mg, 2 mg and 4 mg. Baricitinib improved clinical signs and symptoms in patients with moderate to severe AD and produced a rapid reduction of pruritus. The drug's safety profile was consistent with previous clinical studies with baricitinib in AD. The study is ongoing and new summaries of further results should be expected soon [54].

Upadacitinib

Upadacitinib is a selective Jak1 inhibitor. Results of the phase 2b study, planned for 88 weeks in adult patients with moderate and severe AD, showed a significant effect of the drug on the reduction of itch from day 2 of the therapy [55]. A parallel study involving 167 adult patients with moderate to severe AD reported drug efficacy assessed using the EASI and NRS (pruritus severity scale), IGA scales at all doses, i.e. 7.5 mg, 15 mg and 30 mg after 16 weeks of therapy. A dose-response relationship was observed for the efficacy of Spadacitinib; 30 mg once daily produced the greatest clinical benefit. No dose limiting toxicity was observed [56].

Tofacitinib

Tofacitinib is a non-selective JAK 1/3 inhibitor. It was administered orally to 6 patients with moderate and severe atopic dermatitis, causing reduction of symptoms measured by the SCORAD scale without any adverse effects for up to 29 weeks of treatment, and it was applied topically in the form of 2% ointments [57, 58]. Sixty-nine patients with mild to moderate AD were enrolled in the phase 2a study. Results after 4 weeks of topical therapy showed a much greater clinical efficacy of the drug than placebo with an early onset of action (reduction of itch observed after 2 days of therapy) [58].

Ruxolitinib

The efficacy and safety of ruxolitinib (RUX) cream (a selective JAK1 and JAK2 inhibitor) at concentrations ranging from 0.15% to 1.5% was assessed in randomized, controlled phase 2 clinical trials of 307 adult patients with mild to moderate AD. Pruritus disappeared rapidly within 36 h of treatment, quality of life improved with a good drug tolerance [59].

Delgocitinib

Delgocitinib is an inhibitor of JAK 1,2,3 and TYK2. Results of the phase III study in 158 Japanese patients from 16 years of age with moderate to severe AD are available. 0.5% delgocitinib ointment used over a period of 28 weeks was effective and well tolerated [60]. An earlier phase II study in 327 adult patients with moderate to severe adult AD tested the drug at concentrations of 0.25%,

0.5%, 1%, 3% of the ointment applied twice a day. Results showed a significant and rapid improvement in objective clinical symptoms and pruritus severity with a favorable safety profile [61]. Similarly, in the phase II study conducted in a group of 103 children aged 2 to 15 years with the use of delgocitinib at concentrations of 0.25% and 0.5%, twice a day, an improvement in signs and symptoms, and good drug tolerance were demonstrated [62].

Cerdulatinib and gusacitinib

Cerdulatinib, a selective JAK and SYK (spleen tyrosine kinase) inhibitor, is currently in the phase 2 clinical trials using 0.4% topical gel and shows a reduction in clinical symptoms measured using the EASI scale [63].

Gusacitinib is another JAK/SYK kinase inhibitor in the phase 1b RCT. It is used at the oral dose of 20 mg, 40 mg and 80 mg versus placebo for 4 weeks in 36 patients with moderate to severe AD. Results after 4 weeks of treatment showed high effectiveness and quick onset of action [64].

Conclusions

Presented results of studies of new monoclonal antibodies and small molecules appear to be promising, but long-term safety and efficacy studies in larger groups of patients are still absent. Considering the complex etiopathogenesis of AD, endotypic and phenotypic differences, the prospect of having modern drugs for topical, oral and parental use in the therapeutic portfolio for both pediatric and adult groups in the near future is encouraging.

Currently, for the treatment of patients from 12 years of age with moderate to severe AD who do not respond to topical treatment, we recommend the use of dupilumab. Treatment should be initiated by physicians experienced in the diagnosis and treatment of AD.

Conflict of interest

The authors declare no conflict of interest.

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